ROLE OF RADIONUCLIDE BONE SCAN IN EARLY BREAST CANCER

This dissertation is submitted to

THE TAMIL NADU

DR MGR MEDICAL UNIVERSITY

In partial fulfilment of the university regulations for

M.Ch (Branch VII)

SURGICAL ONCOLOGY

Degree Examination, August 2014

COLLEGE OF ONCOLOGICAL SCIENCES

CANCER INSTITUTE (WIA)

ADYAR

CHENNAI- 600 020

AUGUST 2014

Certificate

*This is to certify that the dissertation entitled "**Role of Radionuclide Bone Scan in early breast cancer**" is a bonafide work done by Dr Saurabh Gupta, College of Oncological Sciences, Cancer Institute (W.I.A) in partial fulfilment of the university rules & regulations for award of M.Ch Surgical Oncology under my guidance & supervision during the academic year 2011 – 2014.*

Guide: *Signature:*

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Certificate

This is to certify that ***Dr.Saurabh Gupta*** *has carried out all relevant work in connection with his dissertation entitled "****Role of Radionuclide Bone Scan in early breast cancer****" under my guidance and supervision. His approach to the subject has been sincere, scientific and analytical.*

This work is recommended for the award of degree ofM.Ch (surgical Oncology) submitted to The Tamil Nadu Dr M.G.R Medical University, Chennai.

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A Word of Gratitude

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Dr Saurabh Gupta

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INTRODUCTION

Use of radionuclides to image the skeletal system for early detection of focal pathology is referred to as bone scan. Bone scan can pick up the asymptomatic alterations in the skeletal system much earlier than their appearance on conventional radiographs. Bone scan is used in multiple pathologies concerning the skeletal system such as in detection of primary bone cancer, cancers spread to bone from other primary sites, skip lesions or involvement of multiple bones. Bone scans can also be useful in detecting different benign conditions of bone likeinflammation or infection causing bone destruction or pathological fractures. Bone scan has an advantage over other conventional imaging modalities in that it images the entire skeletal system and also considers the aspect of remodelling & bone mineralization, thus acting as a functional imaging modality rather than simply imaging the anatomy. 5-15% change in the turnover of bone can be picked up by bone scan, irrespective of the pathology.Radiation exposure by a single bone scan is 6.3 mSv.This is

far less as compared to a CT scan (3.5-25 mSv) or a PET CT (22-23 mSv) [1].

Bone scan utility in early breast cancer is a topic for debate. Bone scan is a very sensitive imaging modality for detection of skeletal metastases, but its specificity is comparatively low.

Various series have reported the false positivity around 10-22%and the false negative rate up to 10%. The false positivity can be due to multiple factors such as the type of equipment, technique of scanning, expertise of the reporting physician and also on the subsequent work up of the areas of abnormal uptake.

In a study by Robinson Baker et al[2], radiographs confirmed metastases in only 1.5% of the stage I & II breast cancer patients with baseline abnormal bone scan. None of the patients with uptake in baseline bone scan, but non confirmatory radiographs,progressed over the follow up period. Many authors do not recommend baseline bone scanning in early breast cancer due to its low pick-up rate and hence, poor cost effectiveness [3-6]. They advocate in favour of staging bone scan in stage III or IV breast cancers. Bone scan results can be of

prognostic value. Few studies reported that patients with baseline positive bone scans are more prone for skeletal relapse subsequently [6,7]. Various studies in the past have reported positivity of bone scans in clinical stage I carcinoma breast ranging from 0-18% and that in stage II upto 0-41%[3]. Bone scans also cannot predict which of the patients in stage I or II of breast cancer will ultimately develop skeletal metastases. With refinement in imaging techniques, bone scan positivity has significantly reduced in T1 & T2 breast cancers.

Present study is being done to assess the usefulness of bone scan as a staging investigation in early breast cancer.

AIMS & OBJECTIVES

To identify the utility of baseline bone scans in early breast carcinoma by studying its:-

- impact on initial treatment decision
- Positive Predictive value
- usefulness as a baseline test for future comparisons

MATERIAL & METHODS

This study was done in the Department of Surgical oncology of Cancer Institute after the approval of ethical committee.

Study Design: This is a retrospective observational study of all stage I & II breast cancer patients who had baseline bone scan & were treated at the institute between the years 2000 to 2004 and followed up for 10 years.

Inclusion Criteria: All new breast cancer patients with cT1/T2 & N0/N1tumors, according to AJCC (7^{th} edition) indexed between 2000–2004 and undergoing a baseline bone scan were included.

Exclusion Criteria:

- Patients with cT3/T4 or cN2/N3 tumours.
- Patients presenting after surgery, done elsewhere, for breast lump (Lumpectomy/Excision biopsy/mastectomy)
- Patients with early breast cancer, not undergoing a baseline bone scan test.
- Patients not completing the planned treatment.

Primary End Point: Positive predictive value of Bone Scan

Secondary End Point: Overall Survival / Disease free survival.

Material & Methods: Case records of all the early breast cancer patients who were treated at the institute between Jan1, 2000 to Dec 31, 2004 were studied for the pattern of bone scan uptake. Patients had a preoperative baseline bone scan performed 3-4 hours after injection of 25mCi of 99mTc-labeled methylene diphosphonate. All scans were reported by a nuclear medicine consultant. Plain radiographs/CT or both were taken of areas of increased tracer uptake. The criteria for considering a bone scan as positive was that if complimentary imaging studies like plain x-rays or CT scan were confirmatory for the site of uptake in bone scan or in due course of time, patient relapses in the site of initial bone scan uptake.Patients were regularly followed-up, and the time and site of any relapse was recorded. The AJCC TNM system (7^{th} Edition) for clinical staging and tumoursize (T) was used.

REVIEW OF LITERATURE

Breast Cancer poses a major public health problem throughout the world for women. The age specific incidence rates for breast cancer increases with age.

In India, according to the tumour registries of all the metros, breast cancer is the most common cancer in women. According to Madras Metropolitan Tumour Registry (MMTR)[8], the Crude incidence rate (CIR) & Age standardised rate (ASR) of carcinoma breast was as follows:

MMTR		1982-87	2000-05	2006-10
Carcinoma Breast	CIR	14.4	28.0	34.2
	ASR	19.1	30.5	33.9

In Delhi, Mumbai & Kolkata the Age adjusted rates were 32.3, 30.1 & 25.5 respectively in the year 2006-08.

It is also the most common cancer diagnosed in women in United States and the second most common cause of cancer death. In 2006, about 274,900 new cases of carcinoma breast were diagnosed in United States and about 40,970 patients died due to this cancer. Incidence rates across the world can vary up to four fold, ranging from 27/100,000 in eastern Asia & middle Africa to 96 in west Europe [9]. Breast cancer was also the most common cancer in Europe in 2006, accountingfor 13.5% of all new cancers [10].

The lifetime risk for breast cancer in United States is 1 in 8 women. The risk at the age of 40 years is 1 in 250 and that at 60 years accounts to about 1 in 35 women. Breast cancer not only ranks first among cancer deaths in women in less developed regions (14.3%), but also the second cause of cancer death in more developed regions (15.4%), just behind carcinoma lung [9].

According to the hospital cancer registry-Cancer Institute (WIA), the proportion of breast cancer patients was 15% of total cancer patients registered in the year 1984-88. This percentage increased to 23.2% during 2005-06 and was static at 23.2% in 2009-10 also [11].

The stage wise distribution of breast cancer is as follows

Stage	1980-1989		2003-2007	
	No.	%	No.	%
I	30	1.4	66	2.1
II	447	21.3	1018	32.2
III	908	43.2	1474	46.6
IV	454	21.6	330	10.4
SNP	262	12.5	274	8.7
Total	2101	100	3162	100

Thus, the percentage of early breast cancer patients (stage I & II) has increased from about 22.7% in the early 80's to about 35% in 2010. The SEER data 1990 also suggest an increase in stage I breast cancer from 25% to about 50% of the invasive cancers from the year 1983 to 1990.

Since 1990, the breast cancer death rates have reduced significantly, both in US (decreased by 24%) and other countries [12,13].This can be attributed to widespread use of screening mammograms and the introduction of better adjuvant chemotherapy and use of tamoxifen.

Due to its high prevalence and prolonged course, breast cancer has always been a favoured topic for study. As early as the last decade of 19th century, Halstead described breast cancer as a localised disease at presentation that spread contiguously in an orderly manner directly via the lymphatic spread, first to axillary nodes and then to distant sites. He proposed that even vertebral or abdominal metastases are also due to contiguous lymphatic spread and thus a radical surgery can halt the spread of breast cancer by removing all the localised disease. This concept remained unchallenged till the mid-20th century when Dr Bernard Fisher proposed the systemic theory stating that carcinoma breast is a systemic disease from the time of presentation. The axillary Lymph nodes are also an indicator of distant spread and thus, a radical surgery or any other local treatment is unlikely to improve overall survival. This paved way for modified radical mastectomies and later on breast conservation. A third hypothesis, known as the Spectrum theory, was put forth by Samuel Hellman in 1994 suggesting carcinoma breast as heterogeneous diseaseconsisting of a spectrum of proclivities with localised disease at one end and metastatic disease on the other end. He proposed that lymph node metastases suggest a

more virulent biology of the tumour and thus high propensity for distant metastases.

EARLY BREAST CANCER (EBC):

Early breast cancer involves tumour in the breast measuring not more than 5cm with or without discrete lymph nodes in the axilla. This consists of stagesIA,IB,IIA& IIB of AJCC staging for carcinoma of breast (7^{th} Edition).

Tubiana et al [14-16], at Institute Gustave-Roussy, studied 3000 breast carcinoma patients before the advent of routine adjuvant chemotherapy and showed that metastatic potential & tumour grade was directly proportional to the size of primary tumour.

A series from MSKCC [17] analysed T1N1 & T1N0 breast cancer patients presenting to them between 1965 & 1970 and found that amongst the node negative patients, 12% patients with tumour <1cm recurred and the recurrence rate was 26% in patients with tumour size between 2-3cm. Thus, about 88% patients with tumour size <1cm could be treated effectively with loco-regional treatment

alone. Another analyses from Chicago suggested 79% cure rates with loco regional therapy in patients with node negative T1 lesions.

In patients with positive axillary nodes, the number of nodes involved is a major indicator of prognosis. In the same MSKCC series mentioned above [17], loco-regional therapy was curative in 68% of patients with T1 tumours and 1-3 axillary nodes positive. The Chicago series also reflected same results. The survival was unchanged if only 1 node was involved in patients withT1 tumours. Even with 2 or 3 nodes being positive, 73% patients with T1 lesion were alive after a follow up of 20 years without any relapse.

As discussed, early breast cancer generally has an excellent prognosis with treatment. The 5yr overall survival for stage I breast cancer can be upto 88% & for that of stage IIA is about 81% [18]. However, as a result of improved diagnostic techniques & newer therapeutic options, survival rates are expected to improve.

CARCINOMA BREAST & BONE METASTASES

Bone health & its maintenance has become an integral part of the multimodality treatment of breast cancer. Bone is the commonest distant metastatic site in carcinoma breast. It is estimated that of all the metastatic breast cancer, about 47 to 85% will have bone metastases [19]. Common bones which have a prelidiction for metastases include spinal column (especially lower dorsal vertebrae),pelvis,ribs,skull and long bones because of the presence of highly vascular red marrow [20]. Typically, skeletal metastases have both osteolytic&osteoblastic components, with preponderance of osteolytic component [21]. Even in pure osteolytic appearing lesions, there is an associated osteoblastic component which is responsible for increased radionuclide uptake in bone scan and detection of metastases. Pure lytic lesions can be missed on bone scan.

Normal Bone Remodelling- The bone micro-environment:

Besides protecting the vital organs and providing support, bone acts as reservoir of various growth factors & calcium, phosphorus which are

released during the process of bone remodelling. The bony skeleton is always undergoing remodelling. There is a balance between the bone forming & resorption process. Remodelling of bone is described as a cyclic process starting with bone resorption and ending with deposition of bone.Cells involved in the process are osteoclasts, the bone degrading cells and osteoblasts,the bone forming cells.Mesenchymal stem cells give rise to cells belonging to osteoblastic lineage, which include osteocytes,bone lining cells and osteoblasts. Bone lining cells are relatively undifferentiated cells which line the bone. Exact function of these cells is unclear. Their retraction is required to start the process of bone resorption [22].

Osteoblasts produce the macrophage colony stimulation factor & Receptor Activator of Nuclear Factor kB ligand (RANKL) which attaches themselves to their respective receptors,i.e, f-cms& RANK on the precursor osteoclast cells and activate their differentiation. Osteoblast cells also produce osteoprotegrin (OPG) which binds to RANKL by acting as a decoy receptor for them and thus prevents activation of osteoclasts. Thus,the ratio of RANKL and OPG determines the degree of osteoclastic activity. The activated

osteoclasts then attaches to the surface of the bone and creates a resorption lacuna where in proteolytic enzymes like cathepsin K and other acids are released and causes degradation of bone matrix. In response, the preosteoblasts are recruited to the site of bone resorption and get differentiated into mature osteoblasts,which then produce osteoid consisting of chondroitin sulphate,collagen,osteonectin& other non-mineral molecules which mineralize over several months [23].

Bone microenvironment in presence of skeletal metastases:

The breast cancer cells reach the bone via haematogenous spread,most commonly to the vertebral bodies via the Batson's prevertebral venous plexus. Once within the bone micro environment, these cancer cells produce several growth factors,most important of them is the parathyroid hormone related protein (PTHrP) [24]. PTHrP can cause up regulation of RANKL and down regulation of OPG [25], causing osteoclast activation and bone resorption. Other growth factors which are stored in the matrix are also released,such as transforming growth factor-B (TGF-B), insulin like growth factors (IGF's), vascular endothelial growth factor (VEGF), fibroblast derived factors and

calcium. These growth factors can cause stimulation & proliferation of tumour cells leading to more production of growth factors &PTHrP and thus,in turn,more degradation of bone matrix and perpetuation of the metastatic cycle. Various cytokines like IL-6,IL-8,IL-11 are also secreted by tumour cells and cause differentiation of osteoclasts and bone resorption.

Natural History of Bone Metastases:

It is estimated that among the patients with breast & prostate cancer who develop distant metastases, about 65-75% will eventually develop metastases in bone [26,27]. Patients of breast cancer with bony metastases are more prone for skeletal complications. Carcinoma breast patients with skeletal metastases have a prolonged median survival of about 24-30 month, which renders them more susceptible to develop skeletal related events (SRE)[28]. These include pathological fractures of the involved bone, spinal cord or nerve root compression (due to pathological fracture or vertebral instability),hypercalcemia of malignancy, need of radiotherapy for symptomatic bone lesions and surgery for impending fractures.

Hypercalcemia of malignancy can be associated with renal failure,altered mental status or even death. Without bisphosphonate therapy, about 3-4 SRE's can occur in these patients every year [28]. Various factors determine the risk of SRE in patients with bone metastases. These are (a) NTX: N-terminal telopeptide of type I collagen, which is a reliable marker of resorption of bone (b) Number of baseline bone lesions (more than 3 lesions are associated with higher rate of skeletal morbidity) (c) Presence of pain with baseline bone lesions. Site of metastatic lesions within the skeletal system also determines patient's risk of developing skeletal related event. Metastases in spine, pelvis or chest are associated with higher risk as compared to those limited to appendicular skeleton or skull. However, median overall survival was the same irrespective of the site of bone uptake.

Treatment Modalities for Skeletal Metastases:

Local Therapy

1.Radiation: Most of the treatment strategies in case of bone metastases are palliative in nature and aim at symptomatic relief. Many of the metastatic bone lesions are subjected to external beam radiotherapy as this will cause relief of pain and other symptoms by more than 70%[29].

Systemic Therapy

1.Bisphosphonates:

Due to predominant lytic nature of the bone metastases secondary to breast carcinoma, most of the attention was to inhibit osteoclast mediated bone damage.Since many years, bisphosphonates were the standard of care in treatment of bone secondaries. Bisphosphonates are the compounds having a structure resembling inorganic pyrophosphate (PPi). Bisphosphonates have characteristic two carbon-phosphate bonds (Pi-C-Pi) that makes them highly resistant to hydrolysis secondary to the action of enzyme phosphatase. Both bisphosphonates and pyrophosphates selectively bind to the crystals of

hydroxy apatite within the bone and thus concentrate at active bone remodelling site. These compounds are then ingested by bone destroying osteoclast cells causing them to undergo apoptosis & thus, prevent loss of bone mass [30].

Bisphosphonates are of two types: Nitrogen containing & Non Nitrogen containing. The examples of non-nitrogen containing bisphosphonates are Etidronate, Tiludronate&Clodronate and that of nitrogen containing are Pamidronate, Olpadronate, Ibandronate, Risedronate&Zoledronate. These nitrogen containing bisphosphonates bind to & blocks an enzyme known as Farnesyl diphosphate synthase (FPPS) functional in 3-hydroxy-3-methyl-glutaryl-CoA reductase **(**HMG-CoA reductase) pathway, leading to inhibition of downstream metabolite formation (geranylgeraniol&farnesol) which maintains cytoskeletal stability. Thus, the osteoclasts undergo apoptosis after ingestion of these diphosphonates bound to the surface of bone [31].

Only intravenous pamidronate&zoledronate have been approved by US FDA for use in patients with carcinoma breast &bone

metastases. Europe has approved oral & IV ibandronate and also oral clodronate for use in these patients.

IV Pamidronate: Two randomised, multicentre, placebo controlled trials established the safety & efficacy of intravenous pamidronate [32,33]. In each trial, pamidronate was shown to cause decrease in the incidence & onset of skeletal related events (SRE) {SRE was defined as spinal cord compression, pathological fracture, requirement of radiation for bone pain or surgery for treatment/prevention of fracture}. Pamidronate was associated with (a) reduction in the proportion of patients having more than 1 SRE (51% as compared to 64% in placebo arm) (b) median time for development of first SRE being extended by 6 months (12.7 months vs 7 months) (c) reduction in the rate of mean skeletal morbidity (2.5 vs 4.0 SRE per year) [34]

IV Zoledronic acid: The effectiveness of zoledronate in decreasing the SRE risk in patients with breast carcinoma was far more when compared to pamidronate [35-37], about 20% additional over what is achieved by using pamidronic acid ($p=0.025$).

Bisphosphonates are generally tolerated well. They can cause jaw osteonecrosis, twice more commonly in the mandible than in maxilla. This is secondary to prolonged intravenous use in cancer patients. Bisphosphonates can, very rarely, cause alteration in renal function. Less than 1% of breast cancer patients, who had received zoledronic acid for up to 2 years, had severe elevation in serum creatinine levels [35]. As the onset of SRE's can cause fall in the quality of life (QOL) of the patients, bisphosphonates also have a favourable impact on the QOL of breast cancer patients.

Research is now on to study the direct antitumor effect of bisphosphonates, mainly zoledronic acid. It is proposed that along with chemotherapy, bisphosphonates have a synergistic effect on the tumour in breast cancer patients, causing decrease in burden of tumour in the skeleton by causing death of tumour cells [38,39]. They may also delay or even prevent bone metastases in early breast cancer patients.

2. Denosumab: It is a human monoclonal antibody to RANK Ligand that binds to RANKL and prevent it to activate the precursor

osteoclasts. In a clinical trial by Stopeck[40], denosumab was found to be superior as compared to zoledronate in preventing skeletal related events in breast,multiple myeloma and prostate cancer patients. FDA has recently approved this drug for treating osteoporosis in women having high risk of fractures.

3.Teriparatide: This drug, the amino-terminal 34 amino acid of parathyroid hormone, acts on osteoblasts and stimulates formation of bone. However, its use can cause increase in the incidence of osteosarcoma and exacerbation of skeletal metastases due to its bone turnover effect[41].

BONE SCAN

Bone scans are commonly used to screen the skeletal system for detection of bone metastases in patients with cancer. A minimum of 50% decalcification should occur before a bony lesion is visible on a plain x-ray. However, bone scan can detect the same lesion with decalcification as little as about 10-15%. Bone scintigraphy and conventional radiology are complementary to each other. Alterations in mineral content of the bone leading to anatomical changes are demonstrated by radiographs whereas bone scintigraphy reveals the changes in metabolic status secondary to alteration in osteoblastic activity & vascularity of bone.

In cases where bone scan suggests metastases but the plain x-ray of the region of interest is normal, there is high possibility of the x-rays becoming abnormal within 12 to 18 months. Up to 75% of the lesions picked up by bone scan will develop corresponding radiographic changes by the end of 6 months. Strender et al found that 8% of breast cancer patients with normal baseline bone scan will eventually develop metastases in bone. Corresponding proportion

after 36 months was nearly 15% [42]. The chances of malignancy in bone scans with solitary rib uptake is less than 50% while it increases to 68% if the solitary uptake is noted in axial skeleton.

After the introduction of PET CT, its use has greatly increased as a staging tool, more commonly in patients with some uptake in baseline bone scans. Studies have shown that the sensitivity of PET CT is similar to that of bone scan but it is much more specific. The sensitivity of PET CT and conventional imaging (including CT/USG/Scintigraphy/X-rays) was 97.4% vs 85.9% respectively ($p=0.009$) while the specificity of these two modalities was 91.2% vs 67.3% ($p=<0.001$) [43]. When compared to bone scan, PET CT better detects osteolytic lesion while bone scan is superior in detection of osteoblastic lesions. Ohta et al studied bone scan and PET CT in detection of bone metastases in patients with breast carcinoma and found that the accuracy, sensitivity and specificity of PET CT was 94.1%, 77.7% & 97.6% respectively while it was 80.3%, 77.7% & 80.9% respectively for bone scan [44].

As mentioned above, conventional imaging is complementary to bone scan and any suspicious uptake in the bone scan should be confirmed using imaging like CT/MRI or PET-CT. If there is associated cortex breach & the site is easily accessible, then a guided or open biopsy can be considered for confirmation of metastatic nature of the lesion.

In the past, various agents have been used for the performance of radionuclide bone scans such as strontium-87, Gallium-67, Fluoride-18 and Thallium-201. A new agent for imaging of bone, known as 99m Technetium labelled stannous tripolyphosphate, was introduced in 1971 by Subramanian and McAfee. Gradually, Methylene diphosphate (MDP) &hydroxy methylene diphosphate (HMDP) became the most commonly used agents for bone scintigraphy. The reason for their popularity was rapid clearance from the blood stream & higher affinity for skeletal system. After these agents are injected intravenously, they are distributed in the compartment of extra cellular fluid. Bone accumulates a major proportion of the dose injected (about 58% of the MDP after 1 hour of injection) and the remaining gets excreted in the urine. Multiple

factors govern the uptake of these tracer agents into the bone, such as changes in flow of blood or capillary permeability, increased surface area of the bone and formation of reactive new bone. Majority of pathological events, including fracture, infection or metastases, initiate an osteoblastic response leading to increased uptake of tracer agent.

Indications of Radionuclide Bone Scan: There is a wide range of indications for bone scan extending in the fields of orthopaedics, sports medicine & rheumatology. Major indications in oncology are listed below:

1) To screen patients having cancers that are prone for metastatic spread to bones (e.g. lung, kidney, breast or prostate cancers)
2) To further evaluate suspicious skeletal radiographs
3) To assess viability of bone as in cases of vascularised free bone grafts
4) Response of the skeletal system to various therapies like chemotherapy or radiotherapy can be assessed using serial bone scans

5) To assess the nature of bone involvement- monostotic or polyostotic.
6) To localize sites for obtaining biopsy.
7) To know the extent of primary bone tumour.

Procedure of Bone Scan: 99m Tc-MDP is used in a dose that varies as per the policy of the department. Usually, the dose ranges from 20-30 mCi (740 – 1110 MBq). In our institute, we administer 25 mCi of the tracer and images are obtained after 3-4 hrs of injection. The equipments required are a scintillation camera and a single/dual head whole body collimator. In cases where a localised pathology is suspected (e.g osteomyelitis) or the bone viability is in question, 3 phase bone scans are performed. Different phases of bone scan are:

1) Dynamic Flow phase: The agent in injected with the patient under the gamma camera and images are obtained every 3-5secs for 1 minute.
2) Blood Pool phase: Images are obtained with 2,00,000 to 5,00,000 counts for the evaluation of degree of vascularity in the region of interest.

3) Static View Phase/Delayed phase: Images obtained after 2-4 hours of injection
4) Sometimes images are also obtained after 24 hours of injection & this is known as the fourth phase.

Normally, approximately 50% of the injected dose of tracer gets localized within the bone and the remaining 40-50% is excreted via the kidneys into the urine. Hence, the kidneys & urinary bladder are visualized in most of the scans. In cases with extensive bone metastases where most of the tracer is taken up by the metastatic lesions and nothing gets left behind for the kidneys to excrete, the kidneys & bladder are not visualized & such scans are referred to as Super scan.

Precautions to be taken while performing the scan:

1) Though the radiation exposure with bone scan is minimal to the patient, universal precautions should be taken by the health care professional performing the scan.
2) Patients should be encouraged to drink plenty of fluids during the waiting period after injection of the agent. This will reduce

the back ground activity by decreasing the soft tissue uptake of the agent and improving renal excretion.

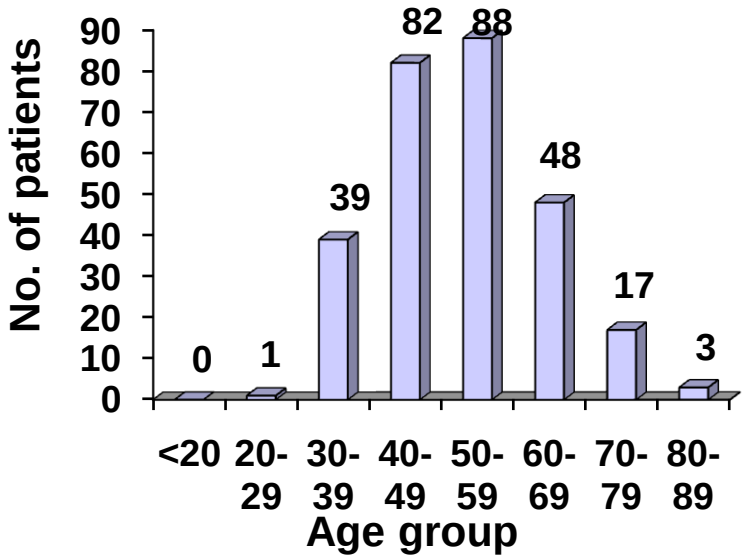
3) Patients are advised to void immediately prior to image acquisition, so that the urinary bladder is emptied and pelvic bones are not obscured.
4) Any attenuating material like belts, buckles, keys or badges should be removed from the region of interest.
5) In cases of painful bony metastases, adequate analgesia should be ensured so that patient can lie down for image acquisition & movement artefacts can be minimized.

A complete history & the relevant clinical details should be known before interpreting a bone scan. Areas that normally show uptake in a bone scan are the epiphyseal growth plates & joints (depending upon the age and metabolic status of the patient). Children may show uptake in skull suture lines at the time of their closure, but it becomes normal once the sutures are closed. Purely osteolytic lesions like Eosinophilic granuloma & Multiple myeloma are not picked up by bone scan.

RESULTS

1. AGE DISTRIBUTION

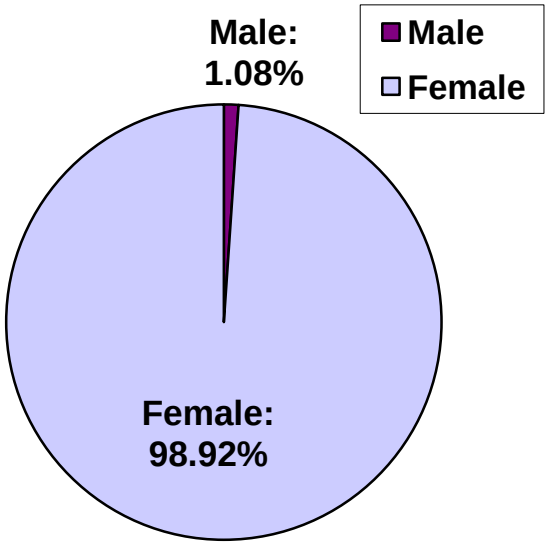
S.No	Age Group (Years)	No. of Patients(%)	No. of patients with Bone Scan uptake(%)
1	< 20	0 (0)	0 (0)
2	20 – 29	1 (0.36)	1 (0.89)
3	30 – 39	39 (14.02)	9 (8.03)
4	40 – 49	82 (29.50)	22 (19.64)
5	50 – 59	88 (31.65)	43 (38.40)
6	60- 69	48 (17.27)	26 (23.21)
7	70 – 79	17 (6.11)	9 (8.03)
8	80 – 89	3 (1.08)	2 (1.78)
9	TOTAL	278 (100)	112 (100)



- Incidence wise, 61% of the total study population was between 40-59 years of age. However, patients between 50-69 years of age constituted about 61% of the total patients with positive baseline bone scan. Patients on either extreme of age, i.e, <30 years and >70 years constituted only 0.9% & 9% respectively.

2. SEX DISTRIBUTION

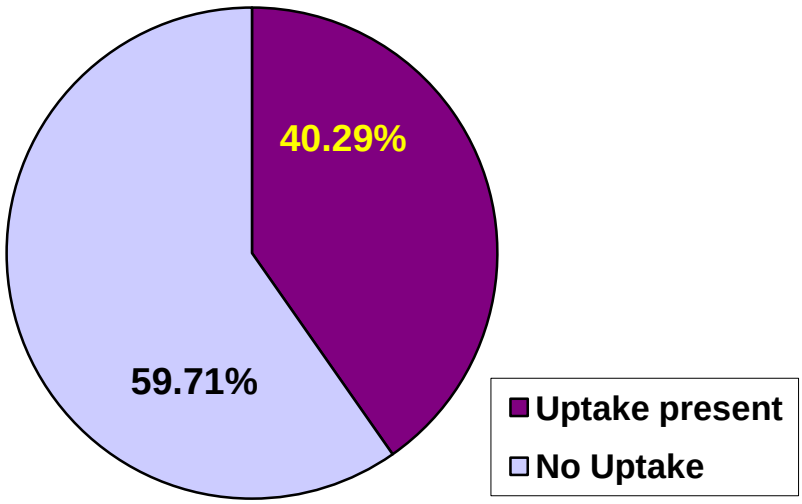
S.No	Sex	No. of patients (%)
1	Female	275 (98.92)
2	Male	03 (1.08)
3.	TOTAL	278 (100)



- Almost 99% of the study population were females. Males constituted only 1.08% of all the early breast cancer patients studied.

3. DISTRIBUTION OF BONE SCAN UPTAKE

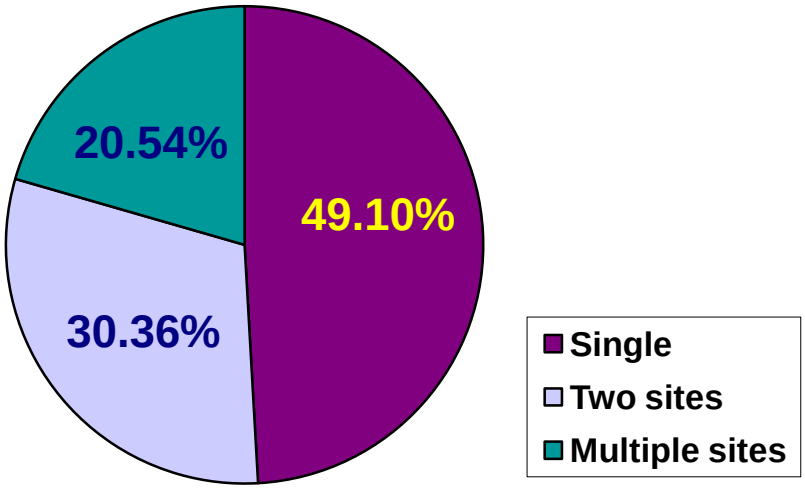
S.No	Uptake	No. of patients (%)
1	Present	112 (40.29)
2	No Uptake	166 (59.71)
3.	TOTAL	278 (100)



- About 40% of total patients with early breast cancer in the study showed an uptake (hot spot) in the baseline bone scan while about 60% patients have normal baseline bone scans.

4. NUMBER OF BASELINE BONE SCAN UPTAKE

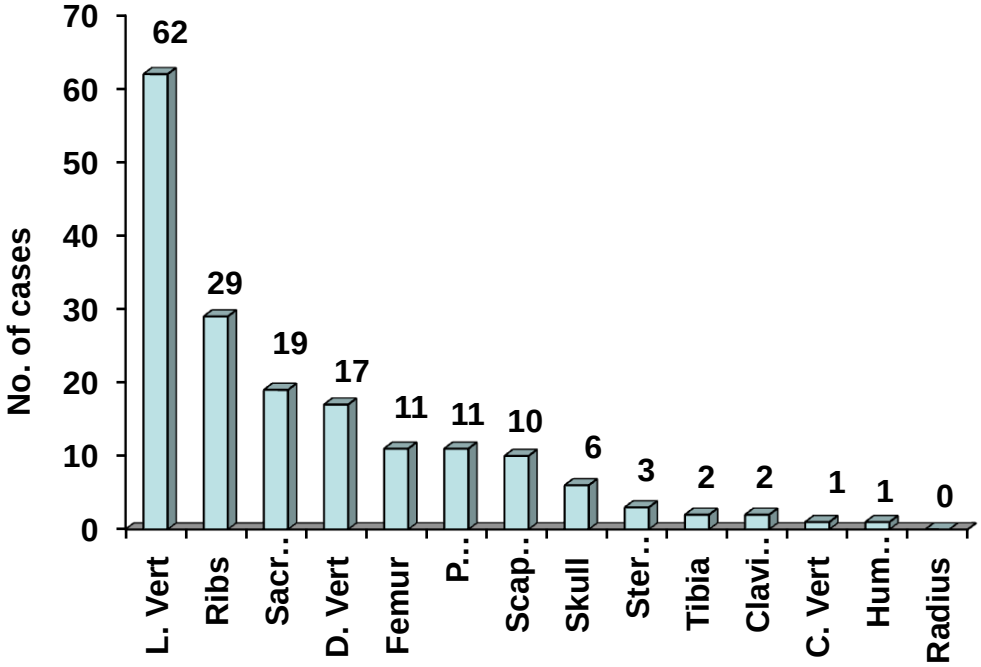
S.No	Uptake	No. of patients (%)
1	Single site	55 (49.10)
2	Two sites	34 (30.36)
3	Multiple sites	23 (20.54)
4	TOTAL	112 (100)



- 79.46% of the patients had uptake in one or two sites on baseline bone scans, while only 20% showed multiple sites of uptake.

5. SITE DISTRIBUTION OF BASELINE BONE SCAN

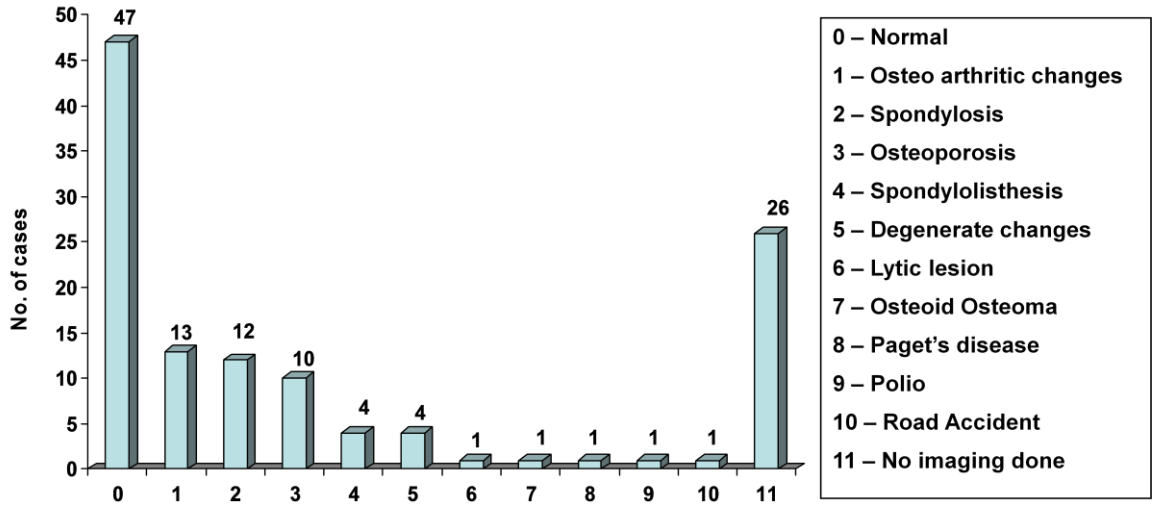
S.No.	Site of uptake	No. of Patients	Percentage (n=112)
1	Skull	06	5.38
2	Sternum	03	2.68
3	Scapula	10	8.93
4	Cervical Vertebra	01	0.89
5	Dorsal Vertebra	17	15.18
6	Lumbar Vertebra	62	55.38
7	Sacrum / S.I Joint	19	16.96
8	Ribs	29	25.89
9	Pelvic Bones	11	9.82
10	Humerus	01	0.89
11	Radius / Ulna	0	0
12	Femur	11	9.82
13	Tibia / Fibula	02	1.78
14	Clavicle	02	1.78
TOTAL PATIENTS		112	100



- 72.34% of the patients had an uptake in the lumbo-sacral region, on initial bone scan. Taking rib uptake into consideration, along with lumbo-sacral uptake, includes 98.23% of the patients (with or without uptake in other sites). Uptake in the appendicular skeleton was seen in 12.50 % of the patients.

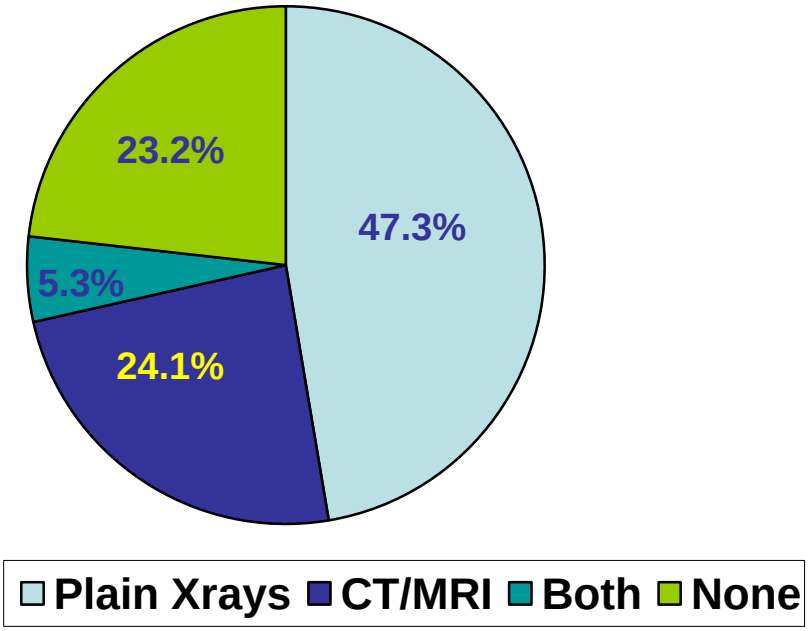
6. CAUSES OF BASELINE BONE SCAN UPTAKE

S.No	Cause of Uptake	No. of Patients	Percentage (n=112)
1	Osteo-arthritic changes	13	11.60
2	Spondylosis	12	10.71
3	Osteoporosis	10	8.93
4	Spondylolisthesis	4	3.57
5	Degenerate Changes	4	3.57
6	Lytic lesion	1	0.89
7	Osteoid Osteoma	1	0.89
8	Paget’s disease	1	0.89
9	Polio	1	0.89
10	Road accident	1	0.89
11	Normal	47	41.96
12	No Imaging done	26	23.21



7. NUMBER OF BASELINE COMPLEMENTARY IMAGING DONE

S.No	Type of Imaging	No. of Patients (%)	No. of Patients with Malignant lesions
1	Plain X-rays	53 (47.3)	0
2	CT/MRI	27 (24.1)	0
3	Both x-rays & CT/MRI	06 (5.3)	0
4	None	26 (23.2)	



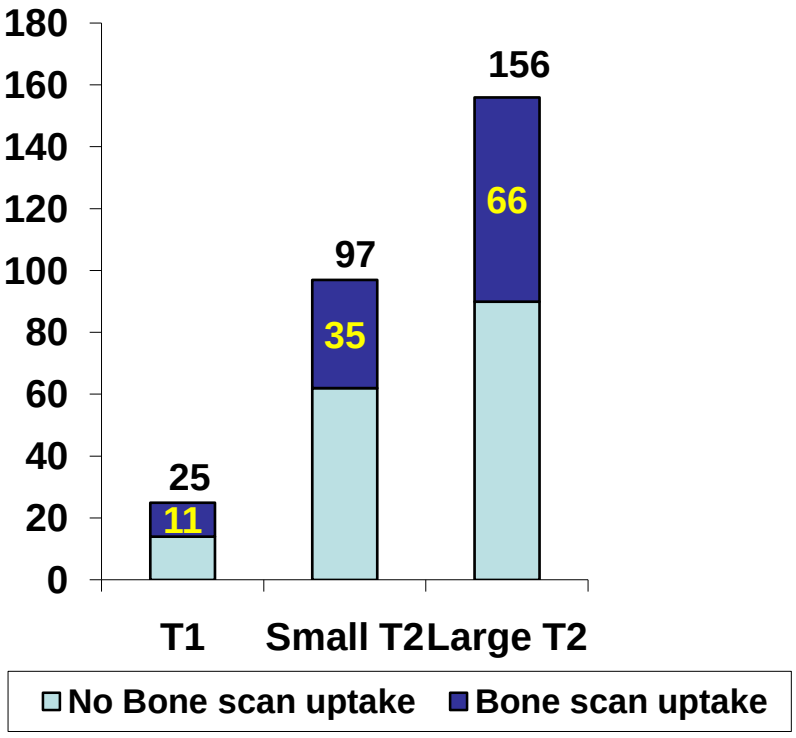
- 86 out of 112 patients (76.78%) with baseline positive bone scan underwent complementary imaging tests for confirmation of site of uptake. 59 patients underwent single or multiple plain x-rays and 33 patients underwent CT or MRI of the site of bone scan uptake. Incidentally, none of the imaging confirmed metastases in any of the uptake in baseline bone scans. Chest x-ray in one patient, with bone scan uptake in right 5^{th} rib, revealed lytic lesion but it was kept under observation and patient did not progress in the follow up period.

8. RELATION OF TUMOR SIZE (T Status) WITH BONE SCAN UPTAKE

S.No	T Status	No. of Patients (%)	Patients with Bone scan uptake (%)
1	T1	25 (9.00)	11 (9.82)
2	Small T2	97 (34.90)	35 (31.25)
3	Large T2	156 (56.10)	66 (58.93)
4	TOTAL	278 (100)	112 (100)

Bone scan & size Cross tabulation

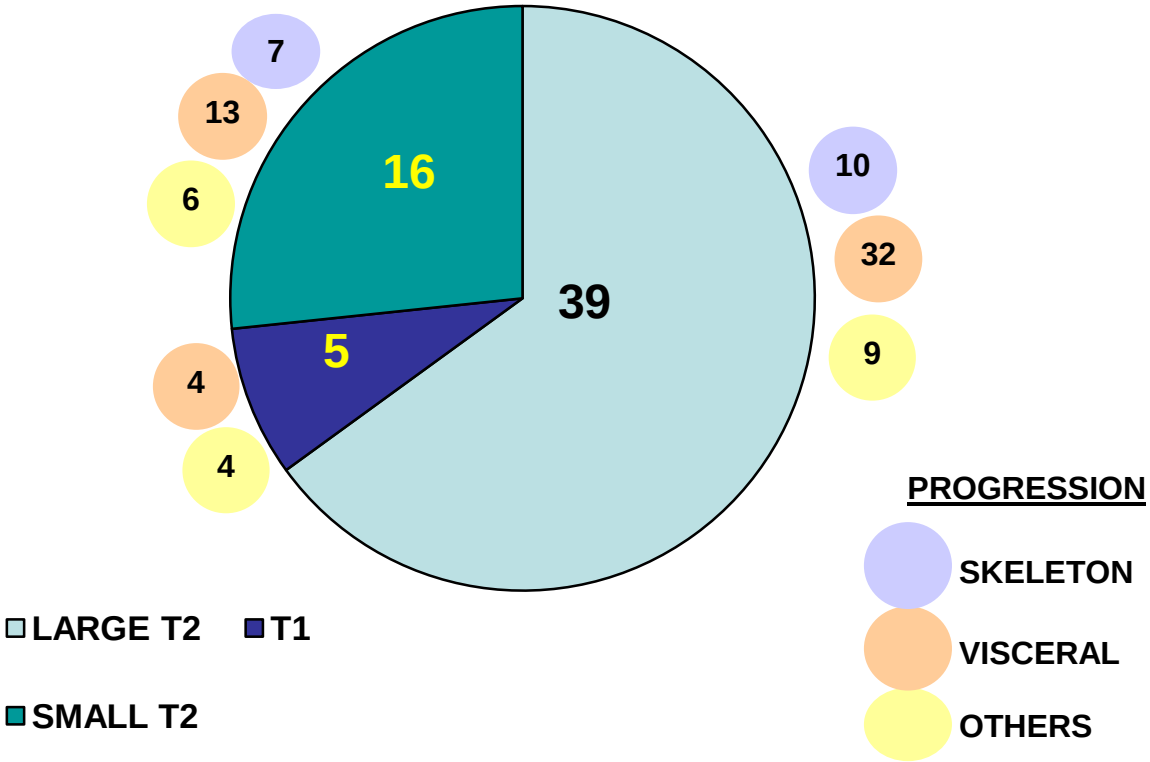
			SIZE			
			T1	SmallT2	LargeT2	Total
Baseline Bone scan	Uptake +	Count	11	35	66	112
		% within size	44.0%	36.1%	42.3%	40.3%
	Uptake -	Count	14	62	90	166
		% within size	56.0%	63.9%	57.7%	59.7%
Total		Count	25	97	156	278
		% within size	100.0%	100.0%	100.0%	100.0%



9. RELATION OF TUMOR SIZE WITH SITE OF PROGRESSION

S.No.	T Status	No. of Patients with progression (%)	Site of Progression	No. of sites	Patients with positive baseline Bone scan
1	T1	5 (20)	Skeleton	0	0
			Visceral	4	3
			Others	4	

2	Small T2	16 (16.50)	Skeleton	7	7
			Visceral	13	
			Others	6	
3	Large T2	39 (25)	Skeleton	10	18
			Visceral	32	
			Others	9	
	TOTAL	60 (21.58)		85 sites	28



'Others' include relapse in the loco-regional sites, opposite breast or in mediastinal nodes

- For analyses T2 was divided into small T2 (more than 2 cm but not more than 3cm) and large T2 (more than 3 cm but not more than 5cm).
- T1 comprised of 9% of the study group and about 44% of these patients had a positive base line bone scan. Out of these 11 T1 patients with positive base line bone scan, none progressed in the skeletal system during the follow up period. 5 patients (20%) progressed during follow up, 4 had visceral metastases and 1 failed in the loco regional site.
- Small T2 comprised almost 35% of the study population with 36% of these showing uptakes in base line bone scans. 16.50% of the small T2 population progressed over time. 7 Patients failed in the skeletal system (2 exclusively in bones and other 5 had coexisting visceral/loco regional disease). Of these 7 patients failing in the skeletal system, 4 had positive baseline bone scans, one of the scans showing uptake in the site of final progression (which was initially kept under observation). The other three bone scans had uptake in sites other than the site ofprogression.

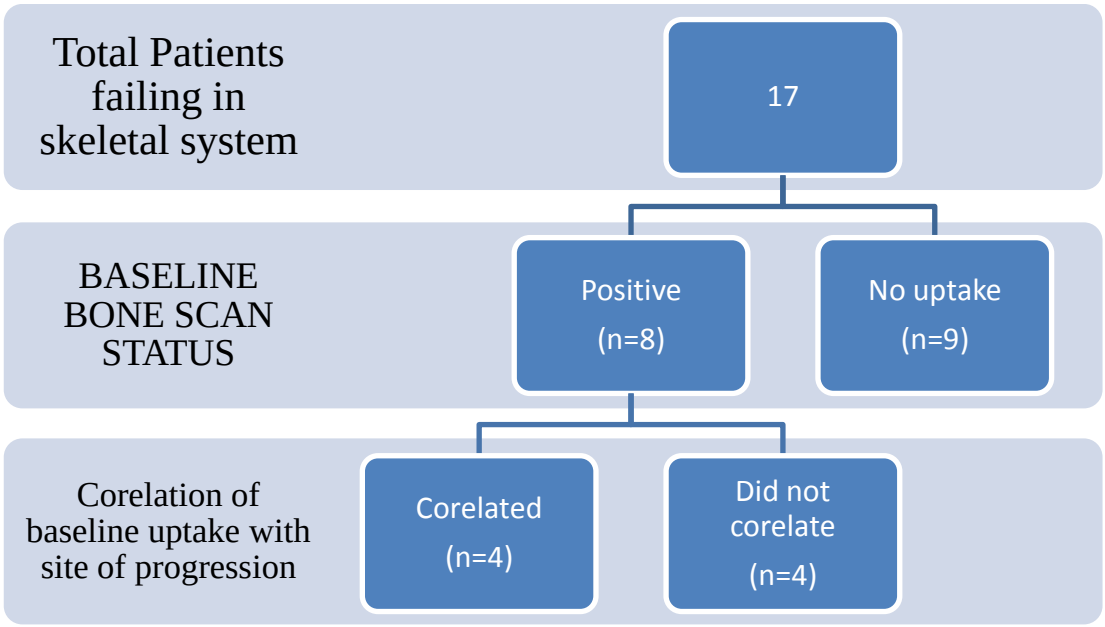
- Large T2 consisted of about 56.10% of the total patients studied with about 42% of these having positive baseline bone scan. 25% of the large T2 patients progressed over time. 10 patients progressed in the skeletal system (7 exclusively in bone and 3 had coexisting visceral metastases). Of these 10 patients, 4 had initial bone scan positive and other 6 had normal baseline bone scans. Of the 4 patients with positive base line bone scans, 1 did not have any follow up bone scan and skeletal metastases in the site of initial bone scan uptake (along with liver metastases) were detected on CT scan in the follow up period, 1 had initial uptake in a site other than the site of ultimate progression. Other two patients had initial uptake that correlated with the site of final progression.

  Thirty two patients had visceral metastases, with or without skeletal/loco regional metastases. Of these, 14 patients hadan uptake in the baseline bone scan which did not progress over time.

10. FOLLOW UP BONE SCANS / IMAGING

Baseline Bone Scan Positive (n = 112)				Baseline Bone Scan Normal (n = 166)			
Follow up BS		Comp. Imaging		Follow up BS		Comp. Imaging	
Not done	74	Not done	97	Not done	129	Not done	156
No uptake	9	WNL	07	Static	25	WNL	4
Improved / Static	14	Positive	08			Positive	6
Progressed	15			Progressed	12		

11. Relation between uptake in baseline bone scan and skeletal progression over follow up.



- Hence, the true positivity of bone scan was = 3.57%
- Of the 4 true positive bone scans, the initial tumour size was small T2 in one (2.5cm) and large T2 in other 3 patients (4cm,4.5cm & 5cm).
- Of these 17 patients with skeletal progression, 10 patients have expired and 7 are alive with disease.

12. DATA OF TRUE POSITIVE PATIENTS

	Age (Yr)	Sex	Size Of Tumor	N Status	Meno-Pausal Status	ER	Baseline Bone Scan	Year	Imaging (Xray/ CT/MR)
1	50	F	5cm	cN1	Post	+	L4,5,S1	2000	Not done
2	47	F	4.5cm	cN1	Pre	-	L5	2002	x-ray WNL
3	54	F	2.5cm	cN0	Post-Hyst	-	L5	2001	CT scan WNL
4	67	F	4cm	cN1	Post	+	D11,L2-5,Rt Femur (h/o TB Spine)	2003	CT Scan No Lytic Areas

	Repeat Bone Scan	Imaging	Year	Rx Given	Further Bone Scan	Last Follow Up	Status
1	Pelvic bones	CT s/o LS spine & Liver mets	2001	Palliative RT	Not Done	May'02	Lost to Follow up
2	L5	PET s/o Left Humerus, Lumbar vertebra mets	2009	RT / Zoledronic Acid / Oral Chemo	2011: Progressive Disease	July'13	Alive With Disease
3	D-L Vertebra	CT s/o Spine & Liver mets	2008	Zoledronic Acid / Oral Chemo	Not Done	Sept'11	Expired
4	Progression	MRI s/o Mets in D11,L4-5 & Femur	2009	RT / Zoledronic Acid	2011: Progression Received Samarium	Dec'12	Expired

DISCUSSION

Ours is a study of patients with early breast cancer (stage I & II) who underwent baseline radionuclide bone scans as a part of metastatic work up. We intend to study how useful these bone scans proved during the treatment and long term follow up of the patients.

Following factors were studied: Age of the patient at presentation, menstrual status, Estrogen receptor status, clinical stage of cancer based on tumour size (cT status), nodal status (cN0 or cN1) and the cause & distribution of baseline bone scan uptake.

Regarding patient characteristics included in our study, almost 99% of the patients were females. The most common age group as far as incidence is concerned, was between 40-59 years of age, which comprised of about 61% of the study population. This was in concordance with a study by Mitsuru Koizumi et al [45] who studied the benefit of baseline bone scans across all stages of breast cancer. The age group between 40-59 years constituted about 65% of all the patients. However, 61.6% of the patients in age group of 50-69 years,

in our study, had uptake in baseline bone scans, making it the most common age group with respect to uptake in baseline bone scans.

Our study had 38.5% premenopausal & 46% postmenopausal women. This was not very much different from that of Mitsuru Koizumi et al [45] where it was 49.3% & 49.8% respectively. Around 15% of our patients had hysterectomy done in the past due to several benign causes & hence their menopausal status could not be ascertained. The percentage of ER positive, ER negative & ER status unknown patients in our study also correlated with previously quoted study [45] (35.9%, 33.4% & 30.6% vs 37.2%, 31% & 31.6% respectively).

The assessment of data regarding nodal status revealed that our cN1 rate was greater than that reported in Japan [45] (61.87% vs 42.8%). Most of the studies of utility of bone scan in breast cancer were done more than 15 years ago [45-48]. These studies considered bone scan as true positive when the site of uptake in the initial bone scan was confirmed by a complementary imaging test (plain x-ray/CT/MRI). In our study, none of the uptakes in 86 of 112 patients could be confirmed by imaging tests (26 patients did not undergo any

further imaging after bone scan). 47.3% of the baseline bone scan positive patients underwent multiple plain x-rays of the sites of uptake, 24% patients underwent either CT or MRI & 5.3% underwent both x-rays & CT/MRI. In a study by Yeh KA et al [47], 316 patients with carcinoma breast (cT1-2 lesions) underwent bone scans during metastatic work up & out of them 63 (20%) had suspicious or positive results on bone scan. This resulted in 101complementary imaging tests (80 plain x-rays, 10 CT scans & 11 MRI) & 4 biopsies. Only 7 patients (2%) were confirmed to have skeletal metastases, most of them presenting with clinical signs of distant metastases. Thisindicatedthe extra burden on the cost of treatment due to the baseline bone scans.

As already discussed in observations, cT2 was divided into small and large T2 based on size (>2cm but not >3cm and >3cm but not >5cm respectively) as proposed by lagrange et al [49]. The proportion of T1, small T2 & large T2 in our study was 9%, 35% & 56% respectively & in Japanese study [45], this was 40%, 34% & 26%. Coleman et al [46] reported 30% & 70% T1 & T2 patients respectively. This shows that a considerable proportion of our early

breast cancer patients had T2 lesions (majority of which were large T2). It is well known that as the size of tumour increases, chances of bone metastases also increases. Incidence of bone metastases in stage I & II was 0.08% , 1.09% and 0%, 3% in the studies quoted earlier [45,46].

The percentage of positive bone scans in Japanese study [45] was 0.23%, 0.55% & 2.26% in T1, small T2 & large T2 tumours respectively. Similar results were reported by Coleman et al, where there was 0.3% & 3% true positivity in T1, T2 lesions. This could not be directly compared to our study results as none of the imaging confirmed metastases in the baseline bone scan & true positivity was calculated based on skeletal relapse over prolonged follow up period. However, in our study also, 59% of patients with uptake in baseline bone scans belonged to large T2 group, reflecting the same results. Over a follow up of up to 10 years, 17 patients had skeletal progression, with or without other sites. Of the 4 patients who had progression in the sites corresponding to the uptake in baseline bone scan, 1patient belonged to small T2 group and 3 belonged to large T2 group. Thus, 1out of 97 small T2 and 3 of the 156 large T2 patients

had true positive baseline bone scans, giving percentage positivity of 1% & 1.92%, similar to that of studies mentioned earlier [45,46]. It is difficult to assign a cut off level of bone metastases beyond which routine bone scintigraphy can be recommended. As newer treatment modalities and targeted agents for bone metastases are becoming increasingly available, more and more bone secondaries can be treated, as a result of which, decision to get a bone scan done lies in the hands of treating physician or as per patient preferences. To help in this decision making, if it is assumed that bone scan can be avoided in patients with risk of bone metastases <1% & it should be done in patients with risk >3%, all our patients with T1 tumours & most of those with small T2 tumours would not have required a baseline bone scan. As the risk percentage in patients with large T2 was 2.26% , 3% or 1.92% in the different studies (including ours), these would fall in the ‘gray area’ where bone scan can be considered if associated high risk features are present, like node positive disease, high grade tumours or poor risk histology. Based on this, if bone scan is not required in patient with T1 or small T2 (3cm or less) tumours, about 44% of baseline bone scans in our study could have been avoided.

Samant R & Ganguly P [48] studied 250 breast cancer patients out of which 25 were detected with metastases at presentation. However, 23 of them had clinical signs or symptoms of distant metastases. Thus, bone scan was useful only in two patients in initial diagnosis of distant metastases. Low yield of baseline bone scan in asymptomatic patients with early breast cancer has also been reported in other studies [50,51] where the incidence of skeletal metastases at presentation was 5% in early breast cancer as opposed to 25% in advanced breast cancer [52,53].

Many centres across the world, including ours, perform radionuclide bone scan in early breast cancer patients as a baseline for future comparison [45,46]. However, when we followed our patients who had uptake in baseline bone scans, 74 patients (66%) never underwent a follow up bone scan and thus the question of future comparison never arose. Nine patients (8%) had no uptake in follow up bone scans, i.e, the initial uptake disappeared. 15 patients (13.4%) had a worsened follow up bone scan report and 14 patients (12.5%) had improved/static report. Also, 97 patients (86.6%), of the ones with uptake in baseline scan, did not undergo any complementary

radiological imaging in the follow up period. 15 patients (13.4%) had a radiological imaging (plain x-rays or CT/MRI) of which 7 patients had normal imaging results (on comparing with bone Scan results, 5 of them had progression, one had static disease & one had improved bone scan report). Out of the 8 patients with imaging suggestive of metastases, 7 had a progression and 1 showed improvement in the follow up bone scan. Thus it can be inferred that bone scan was useful as baseline test for future comparison in only 11 (9.82%) other patients whose follow up bone scans were static as compared to baseline scan and hence no further radiological imaging tests were done in these patients.

Finally, the true positivity of baseline bone scan in early breast cancer patients (stage I & II), in our study was, 3.57%. Coleman et al [46] also reported 4% true positivity across all the stage of breast cancer. Another study by Yeh KA et al [47] reported 11% positive predictive value of baseline bone scans in T1-2 breast cancer patients.

The overall survival & DFS, of our study group, at 5yr and 10 years was 87%,80% and 75%,68% respectively.

CONCLUSION

As a policy, the institute has been performing bone scan for early stage breast cancer patients for the past 15 years. This retrospective analysis shows a low positive predictive value of baseline radionuclide bone scans in this group of patients, especially in those with primary tumour less than 3cms. Also, the usefulness of these scans as baseline test for future comparison proved to be limited to about 10% of the patients.

Thus, we recommend that baseline radionuclide bone scans can be avoided in early stage breast cancer patients except in those who are symptomatic & in patients with primary tumour more that 3cm in size with or without clinically significant axillary lymph nodes.

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